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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/516,078	03/01/2000	Zsolt Istvan Hertelendy, Pharm.D.,Ph.D	45061-8	3549

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CHARLES A. CREHORE
ULMER & BERNE, LLP
1300 EAST NINTH STREET SUITE 900
CLEVELAND, OH 44114

EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/516,078	HERTELENDY, PHARM.D.,PH.D ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,12,18 and 21-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,12,18,21-24 and 26-31* is/are rejected.

7)☒ Claim(s) *25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Claims 7, 12, 18, 21-31 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 04, 2005 has been entered.

Double Patenting

2. Obviousness type double patenting has been obviated through submission of an effective terminal disclaimer over US Pat. 6,099,853. Claims that are anticipated by the allowed claims of US Pat. 6,099,853 include amended or new claims 7, 12, 18, 21-22, 25, 27, 30.

Allowable Subject Matter

3. Claim 25 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

4. Applicant's arguments with respect to claims 7, 12,18,21-31 (amended and new claims) have been considered but are moot in view of the new ground(s) of rejection in light of the extensive amendments and new claim limitations submitted with the claims.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 7, 12, 21-24, 27-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions that comprise a suppository base that comprises both polyethylene glycol and polysorbate together with a microbial pathogen or adjuvants for induction of an immune response, and specific vaccine compositions that comprise whole bacterial pathogens or known vaccine antigens, and viruses excluding HIV virus for induction of a prophylactic immune response, does not reasonably provide enablement for the administration of any vaccine adjuvant (claim 7,21-23 and 27-29), or any suppository composition based delivery system that comprises any whole microbial pathogens (claim 12 , 24, 30-31), or any antigen, or nucleic acid that encodes an antigen derived therefrom for induction of a protective prophylactic immune response and used for the stimulation of a protective immune response that prevents (prophylactic) infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to teach how to formulate and use the claimed vaccines. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to infection or disease induction. The specification teaches various sources for antigens to include viral, bacterial and microbial, and claims any and all whole cellular constituents to induce either

cellular or humoral immune responses for induction of a protective prophylactic immune response.

The specification does not provide substantive evidence that any whole antigen, in any amount, administered to any bodily orifice, to include vaginal administration, or urogenital administration, would be capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing infections caused by a pathogen of a human or animal. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a whole cell microbial composition, albeit a bacterial, viral or microbial cell, to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of a protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Boslego (1991) shows a gonorrhea vaccine that was of a microbial pathogen that induced an immune response, but was not prophylactic, protective upon challenge (see page 212, col. 2, paragraphs 2-5). Orkin et al (1995) is cited to show unpredictability of nucleic acid based vaccines, absent specific guidance.

Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. Cruz et al (Current Pharmaceutical Design, 2004) provides data on the vaginal administration of

whole cell Lactobacillus to prevent HIV viral infection, and found that this composition was ineffective to accomplish the desired protective effect (see Table 1, Vaginal Fortifiers, suppository, page 320; and sections 9.3 and 9.3.1, page 328 "did not improve clinical cure rates" "development was suspended following the failure of CTV-05 to meet its clinical end-point in phase II trials"). Lacombe et al (Vaccine, 2004) teaches a whole cell pertussis vaccine failed to provide prophylactic protection (see page 627, col. 1, Section 4. Discussion "Increasing intensity of exposure to pertussis was associated with a higher failure rate of both vaccines"). Sutjipto et al (Journal of Virology, 1990) teaches that inactivated Simian Immunodeficiency virus vaccine failed to protect monkeys, when the vaccine was administered by a genital mucosal route, from infection. Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful whole cell vaccine without the prior demonstration of vaccine efficacy.

The specification fails to teach the identity of what whole cells, antigens and/or nucleic acids as well as whole cell mutants (definition provided in instant Specification at page 10, paragraph 3), to induce protective immunity, albeit cellular or humoral immunity. Further, the specification fails to provide an adequate written description of what surface antigens, or nucleic acid sequences or whole cell compositions in order to induce a prophylactic immune response to provide a vaccine effect in any human or animal.

The skilled artisan would be required to de novo locate, identify and characterize the claimed whole cells, antigens and nucleic acids (definition provided in instant Specification page 3) now claimed. This would require undue experimentation given the fact that the specification is completely lacking in teachings as to what single whole antigens, mutated whole cell antigens or combinations of whole cell antigens or mutated antigens or nucleic acids that would contain

the claimed characteristics and could be used in a method of inducing an immune response that prevents infection.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 7, 18, 23 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Clancy (US Pat. 4,873,090).

(Instant claim 7) Clancy discloses the instantly claimed invention directed to a suppository (see col. 1, lines 66-67 and col. 2, lines 1-2) base delivery system (see col. 2, lines 8-38) for induction of an immune response (see abstract "killed bacterial gives a better protection"), wherein the vaccine comprises:

a. A vaccine (see col. 1, lines 47-62), or vaccine adjuvant ("whereby each species acts as an adjuvant for the other bacteria", col. 1, lines 62-63) is able to produce a humoral or cellular immune response (see Clancy col. 3, lines 42-45; col. 5, line 5 "antibody levels"); and

b. A suppository base comprising pharmaceutically acceptable amounts of polyethylene glycol (see col. 2, lines 23-24 and 29-30) and polysorbate (see col. 2, "coatings", and col. 6, line 55 "Tween 80" (the registered trademark for polysorbate 80))

adapted for insertion into a human body cavity and to be in contact with tissues of the urogential tract (see Clancy, col. 3, lines 15-18).

By all comparable data, the suppository pharmaceutical composition of Clancy is the same or equivalent composition now claimed as they both comprise the same components recited in the claim, and the composition of Clancy was formulated for administration to the mucosal surfaces (see col. 3, line 16) of a human "urogenital system (see Clancy, col. 3, line 17). No structural or compositional (suppositories, col. 2, lines 1-2) differences are apparent in what is now claimed and therefore inherently (urogenital system includes the term "vagina" of claim 23) anticipates the instantly claimed invention.

(Instant claim 18, 27) Clancy discloses a method that comprises the steps of :

(a) inserting, administering (col. 3, lines 5-14 "administered to a patient" at a "mucosal site to "prevent acute mucosal infections in humans) a vaccine suppository (see col. 2, lines 1-2) into a urogenital (see col. 3, line 17) orifice of a human (ureogenital system of human (see col. 3, lines 6-7 and 17);

(b) contacting the suppository (see col. 2, lines 1-2) with mucosal tissue (see col. 3, lines 15-16) at and internal to the urogenital orifice (rectal administration, col. 2, lines 1-2) to facilitate transfer of the vaccine (title) or vaccine adjuvant (col. 1, lines 62-63) material there through and induce an immune (see col. 3, lines 42-44) response in the human (col. 3, lines 5-14). Clancy anticipates the instantly claimed invention.

9. Claims 7,18, 23, 26-27,29 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter (US Pat. 5,712,257)

(Instant claim 7, 23) Carter discloses the instantly claimed invention directed to a pharmaceutical composition (see col. 5, line 20) formulated into a suppository (see col. 7, lines 32-41) for treatment of urogenital infections (see genitor-urinary system, col. 7, line 36), the suppository base being one that can be administered or inserted into the rectal or vaginal locations (see col. 10, lines 4-5), the base delivery system comprising a mixture of surfactants (see col. 1, lines 39) together with dsRNA (see col. 1, lines 39-40) and microbial pathogen immunogens (see col. 4, lines 61-63 "HIV protein gp120"; and "reconstituted viral envelopes" col. 13, lines 50-51) for induction of an immune response (see col. 13, line 52 "immunological") directed against venereally-transmitted pathogens (see col. 1, lines 53-54; and col. 7, lines 13-31) , wherein the vaccine comprises:

c. A vaccine (see col. 1, lines 15-20, col. 4, lines 61-63), or vaccine adjuvant ("IL-2", col. 8, line 41 and col. 8, lines 25-50); and

d. A suppository base (vaginal or rectal suppository, col. 10, lines 4-5) comprising pharmaceutically acceptable amounts of polyethylene glycol (see "mixtures of surfactants "col. 1, line 39; col. 4, lines 43-47; col. 9, lines 58 "mixed with solutions of various surfactants") polyethylene glycol (col. 10, lines 45-46) and polysorbate (see col. 5, lines 41-63 "polyoxyehtylene esters" and col. 13, lines 10, lines 34-35 "polysorbate 20 and polysorbate 80") adapted for insertion into a human body cavity and to be in contact with tissues of the urogential tract (see Carter "rectal and vaginal suppositories", col. 7, line 39) of humans (see col. 1, line 29 "human")

By all comparable data, the suppository pharmaceutical composition of Carter is the same or equivalent composition now claimed as they both comprise the same components recited in the claim, and the composition of Carter was formulated for administration to the mucosal

surfaces (see col. 14, line 22, claim 6) of a human "urogenital system" (see Carter, col. 7, lines 32-41 "solid or semi-solid preparations" suppositories (both rectal and vaginal)"). No structural or compositional differences are apparent in what is now claimed and therefore anticipates the instantly claimed invention.

(Instant claim 18, 26, 27, 29) Carter discloses a method that comprises the steps of:

(a) inserting ("topically applying" to a "mucous membrane tissue", see claim 6) a vaccine suppository (see col. 7. lines 13-41) into a urogenital (see col. 7, line 39) orifice of a human;

(b) contacting the suppository (see col. 7, line 39 and col. 9, lines 65-67 and col. 10, lines 1-5) with mucosal tissue at and internal to the urogenital orifice (vaginal or rectal administration, (see col. 7, line 39 and col. 9, lines 65-67 and col. 10, lines 1-5) to facilitate transfer of the vaccine material there through and induce an immune (see col. 4, line 56 "facilitate transport across the cell membrane") response in the human ("intracellularly", col. 10, lines 50-52). Carter anticipates the instantly claimed invention.

Conclusion

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

11. Dorland's Medical Dictionary defines Tween to be a trademarked product representative of a family of polysorbate molecules that include) esters of sorbitol ie: "polyoxyethylene sorbitan monolaurate".

12. WO96/07426; EP 0486959; WO9511701; WO97/03655 are cited to show compositions that comprise polysorbate and polyethylene glycol and/or formulations in suppositories, capsules, creams or microparticles.

13. PG-Pub 20050020576; 20020012680 (claims 13-15 and 67); 20030044434 ([0085 – 0091] and claims "cyclosporins") are cited to show compositions that comprise microbial pathogen vaccine components combined with polyethylene glycol and polysorbate.

14. US Pat. 5,776,921; 5858401; 6576633; 6531139; 6121313 ; 5681552; 5679360; 5840771; 6159174; 5002771; 3880,991; 5270,344; 5,189,066; 3773929; 3551554 are cited to show various pharmaceutical compositions that are suppositories and/or comprise polyethylene glycol and/or polysorbate together with additional components.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
June 22, 2005

L. F. Smith

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600